Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Management of Medication Toxicity or Intolerance (Last updated April 14, 2020; last reviewed April 14, 2020)

Panel's Recommendations

- In children who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately **(AIII)**. Once symptoms of toxicity have resolved, ARV therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) **(AII*)**.
- When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; an agent with a different toxicity and side-effect profile should be chosen **(AI*)**.
- The toxicity and the medication presumed to be responsible should be documented in the medical record and the caregiver and patient should be advised of the drug-related toxicity **(AIII)**.
- In general, dose reduction **is not recommended** for management of ARV toxicity **(AII*)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

† Studies that include children or children/adolescents but not studies limited to post-pubertal adolescents

Medication Toxicity or Intolerance

Effective antiretroviral therapy (ART) results in viral suppression and improved immune function. These benefits far outweigh the risks associated with the adverse effects (AEs) of some antiretroviral (ARV) drugs. However, AEs have been reported with the use of all ARV drugs. Currently recommended ARV regimens are associated with fewer serious and intolerable AEs than regimens used in the past. In the mid-1990s when combination ART was introduced, AEs were among the most common reasons for switching or discontinuing therapy and for medication nonadherence (see Adverse Effects of Antiretroviral Agents in the Adult and Adolescent Antiretroviral Guidelines).[1] In recent clinical trials with newer ARV drugs, however, <10% of ARV-treated patients had treatment-limiting AEs.[2-9]

The incidence of some longer-term complications of ART (e.g., bone or renal toxicity, dyslipidemia, accelerated cardiovascular disease) may be underestimated, because most clinical trials enroll a select group of patients based on highly specific inclusion criteria and the duration of participant follow-up is relatively short.[2,4,5,10-13] Unexpected AEs may emerge with additional clinical experience with newer ARV drugs. The prevalence and the relationship of these AEs to newer ARV drugs can be unclear (e.g., weight gain with the use of integrase strand transfer inhibitors [INSTIs]; see Table 15h).[14,15] To achieve sustained viral suppression throughout a child's lifetime, both short-term and long-term ART toxicities must be anticipated. The clinician must consider potential AEs and issues with medication palatability when selecting an ARV regimen, as well as the individual child's comorbidities, concomitant medications, and history of drug intolerance or viral resistance.

The AEs caused by ARV drugs can vary from mild, more common symptoms (e.g., gastrointestinal [GI] intolerance, fatigue) to infrequent, but severe and life-threatening, illness. Drug-related toxicity can be acute (occurring soon after a drug has been administered), subacute (occurring within 1 to 2 days of administration), or late (occurring after prolonged drug administration). For a few ARV medications, pharmacogenetic markers that are associated with the risk of early toxicity have been identified; however, the only marker that is routinely screened for is HLA-B*5701, a marker for abacavir (ABC) hypersensitivity.[16] For certain children aged <3 years who require treatment with efavirenz (EFV), an additional pharmacogenetic marker, cytochrome P450 2B6 genotype, should be assessed in an attempt to prevent toxicity (see the Efavirenz

section in Appendix A: Pediatric Antiretroviral Drug Information).[16-20]

The most common acute and chronic AEs that are associated with currently recommended ARV drugs or drug classes are presented in the Management of Medication Toxicity or Intolerance tables. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies. The tables also include selected references that provide further information about these toxicities in pediatric patients.

As new ARV drugs are approved for use in children, many of the older ARV drugs **are no longer recommended** because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data. The following older ARV drugs have therefore been removed from the Management of Medication Toxicity or Intolerance tables:

- Didanosine (ddI)
- Enfuvirtide
- Fosamprenavir
- Indinavir
- Nelfinavir
- Saquinavir
- Stavudine (d4T)
- Tipranavir

Information on the toxicities that are associated with these agents can be found in archived versions of the toxicity tables and archived drug sections. Because peripheral nervous system toxicity is primarily associated with some of the older drugs that were removed from the toxicity tables (e.g., ddI, d4T), that toxicity table has also been archived.

Management

ART-associated AEs can range from acute and potentially life-threatening to chronic and insidious. Serious life-threatening events (e.g., a hypersensitivity reaction [HSR] to ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life threatening (e.g., urolithiasis caused by atazanavir, renal tubulopathy caused by tenofovir disoproxil fumarate) can usually be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening AEs (e.g., dyslipidemia) can be addressed either by switching the suspected causative agent for another agent or by managing the AE with additional pharmacological or nonpharmacological interventions.

Management strategies must be individualized for each child, taking into account the severity of the toxicity, the child's viral suppression status, and the available ARV drug options. Clinicians should anticipate the appearance of common, self-limited AEs and reassure patients that many AEs will resolve after the first few weeks of ART. For example, when initiating therapy with boosted protease inhibitors (PIs), many patients experience GI AEs such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these AEs. Some patients may require antiemetics and antidiarrheal agents for symptom management. Central nervous system (CNS) AEs are commonly encountered when initiating therapy with EFV. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take EFV-containing regimens at bedtime and on an empty stomach to help minimize these AEs. Patients should be advised that these AEs usually diminish within 2 to 4 weeks of initiating therapy in most people; however, they may persist for months in some patients, and may require a medication change.[21,22] In addition, mild rash can be ameliorated with drugs such as antihistamines. Addressing AEs is essential, as continued use of an ARV agent that a patient finds intolerable may lead the patient to stop their treatment, risking viral rebound and the development of resistance.[23,24]

In patients who experience unacceptable AEs from ART, every attempt should be made to identify the offending agent and to replace the drug with another effective agent as soon as possible.[7,25,26] For mild to moderate toxicities, changing to a drug with a different toxicity profile may be sufficient; discontinuing all therapy may not be required. When interrupting a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, many experts will stop the NNRTI for 7 to 14 days before stopping the dual-nucleoside reverse transcriptase inhibitor backbone, due to the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see Table 15k) should stop all components of the drug regimen simultaneously, regardless of drug half-life. Once the cause of the AE has been determined, clinicians can either initiate a new ARV regimen that does not contain the offending drug or resume the original regimen, if the event is attributable to another cause.

All drugs in the ARV regimen should then be started simultaneously, rather than one at a time, while observing the patient for AEs.

When an ARV regimen is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and side-effect profiles should be chosen when possible.[27-30] Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is only permissible for patients whose viral loads are undetectable.

In general, dose reduction is not a recommended strategy for toxicity management, as inadequate ARV drug levels may lead to decreased virologic efficacy. Therapeutic drug monitoring (TDM) is not routinely recommended; however, it may be used in cases where mild or moderate toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range.[31,32] An expert in the management of pediatric HIV should be consulted when dose reduction is being considered based on the results of TDM. Dose reduction after TDM has been studied most extensively with EFV, since increased CNS toxicity has clearly been associated with higher levels of EFV (see the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information).

To summarize, management strategies for drug intolerance include:

- Symptomatic treatment of mild-to-moderate, transient AEs.
- Switching one drug for another drug that is active against a patient's virus (e.g., switching to ABC for zidovudine-related anemia or to a PI or INSTI for EFV-related CNS symptoms).
- Using dose reduction, guided by TDM, after consulting with an expert in pediatric HIV.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2019. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

2. Arpadi S, Shiau S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child.* 2013;98(4):258-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23220209.

3. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet.* 2013;381(9875):1391-1403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23473847.

4. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc.* 2013;16:18600. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23782481.

5. Purswani M, Patel K, Kopp JB, et al. Tenofovir treatment duration predicts proteinuria in a multiethnic United States cohort of children and adolescents with perinatal HIV-1 infection. *Pediatr Infect Dis J.* 2013;32(5):495-500. Available

at: http://www.ncbi.nlm.nih.gov/pubmed/23249917.

6. Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS.* 2013;27(9):1403-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23343913.

7. Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PLoS One.* 2017;12(2):e0169762. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28192529.

8. Viani RM, Alvero C, Fenton T, et al. Safety, Pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatr Infect Dis J.* 2015;34(11):1207-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26244832.

9. Nachman S, Alvero C, Teppler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a Phase 1/2 open label, non-randomised, multicentre trial. *Lancet HIV.* 2018;5(12):e715-e722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30527329.

10. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad.* 2018;4(2):72-79. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29682298.

11. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV.* 2018;5(6):e291-e300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29731407.

12. Arrive E, Viard JP, Salanave B, et al. Metabolic risk factors in young adults infected with HIV since childhood compared with the general population. *PLoS One.* 2018;13(11):e0206745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30408056.

13. Dona D, Mozzo E, Luise D, et al. Impact of HIV-1 infection and antiretroviral therapy on bone homeostasis and mineral density in vertically infected patients. *J Osteoporos.* 2019:1279318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30693083.

14. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis.* 2019;pii:ciz407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31100116.

15. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr.* 2017;76(5):527-531. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28825943.

16. Asensi V, Collazos J, Valle-Garay E. Can antiretroviral therapy be tailored to each human immunodeficiency virus-infected individual? Role of pharmacogenomics. *World J Virol.* 2015;4(3):169-177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26279978.

17. Sinxadi PZ, Leger PD, McIlleron HM, et al. Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. *Br J Clin Pharmacol.* 2015;80(1):146-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25611810.

18. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. *AIDS.* 2017;31(8):1129-1136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28323755.

19. Gallien S, Journot V, Loriot MA, et al. Cytochrome 2B6 polymorphism and efavirenz-induced central nervous system symptoms : a substudy of the ANRS ALIZE trial. *HIV Med.* 2017;18(8):537-545.; Available at: https://www.ncbi.nlm.nih.gov/pubmed/28145050.

20. Soeria-Atmadja S, Osterberg E, Gustafsson LL, et al. Genetic variants in CYP2B6 and CYP2A6 explain interindividual variation in efavirenz plasma concentrations of HIV-infected children with diverse ethnic origin. *PLoS One.* 2017;12(9):e0181316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28886044.

21. Gazzard B, Duvivier C, Zagler C, et al. Phase 2 double-blind, randomized trial of etravirine versus efavirenz in

treatment-naive patients: 48-week results. *AIDS.* 2011;25(18):2249-2258. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21881478.

22. Wynberg E, Williams E, Tudor-Williams G, Lyall H, Foster C. Discontinuation of efavirenz in paediatric patients: why do children switch? *Clin Drug Investig.* 2018;38(3):231-238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29181714.

23. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among US youth with perinatally acquired HIV. *AIDS.* 2019;33(12):1923-1934 Available at: https://www.ncbi.nlm.nih.gov/pubmed/31274538.

24. Swan H, Reisman JI, McDannold SE, Glickman ME, McInnes DK, Gifford AL. The relationship between gastrointestinal symptom attribution, bothersomeness, and antiretroviral adherence among adults with HIV. *AIDS Care.* 2018;30(8):997-1003. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29415554.

25. Davidson I, Beardsell H, Smith B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study. *Antiviral Res.* 2010;86(2):227-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20211651.

26. Strehlau R, Shiau S, Arpadi S, et al. Substituting abacavir for stavudine in children who are virally suppressed without Lipodystrophy: Randomized Clinical Trial in Johannesburg, South Africa. *J Pediatric Infect Dis Soc.* 2018;7(3):e70-e77. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29373687.

27. Valantin MA, Bittar R, de Truchis P, et al. Switching the nucleoside reverse transcriptase inhibitor backbone to tenofovir disoproxil fumarate + emtricitabine promptly improves triglycerides and low-density lipoprotein cholesterol in dyslipidaemic patients. *J Antimicrob Chemother*. 2010;65(3):556-561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20053692.

28. Murnane PM, Strehlau R, Shiau S, et al. Switching to efavirenz versus remaining on ritonavir-boosted lopinavir in HIV-infected children exposed to nevirapine: long-term outcomes of a randomized trial. *Clin Infect Dis.* 2017;13(11):e0206745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28419200.

29. Raffi F, Esser S, Nunnari G, Perez-Valero I, Waters L. Switching regimens in virologically suppressed HIV-1-infected patients: evidence base and rationale for integrase strand transfer inhibitor (INSTI)-containing regimens. *HIV Med.* 2016;17 Suppl 5:3-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27714978.

30. Jao J, Yu W, Patel K, et al. Improvement in lipids after switch to boosted atazanavir or darunavir in children/adolescents with perinatally acquired HIV on older protease inhibitors: results from the Pediatric HIV/AIDS Cohort Study. *HIV Med.* 2018;19(3):175-183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29159965.

31. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit*. 2011;33(3):265-274. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21566505.

32. Vo TT, Varghese Gupta S. Role of cytochrome P450 2B6 pharmacogenomics in determining efavirenz-mediated central nervous system toxicity, treatment outcomes, and dosage adjustments in patients with human immunodeficiency virus infection. *Pharmacotherapy*. 2016;36(12):1245-1254. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27779789.